PATENT SPECIFICATION

(11) 1 397 073

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(21) Application No. 15838/71 (22) Filed 19 May 1971
(23) Complete Specification filed 18 May 1972
(44) Complete Specification published 11 June 1975
(51) INT CL² C07D 271/06; A61K 31/41
(52) Index at acceptance
C2C 1230 1341 1432 1470 1510 1532 1562 1626 200 213 214 215 220 221 222 225 226 227 22Y 246 247 250 251 252 253 254 255 25Y 270 271 27X 280 305 30Y 313 316 31Y 320 324 327 332 338 339 342 34Y 351 354 355 35X 360 361 364 366 368 36Y 373 37X 37Y 386 388 396 397 401 40Y 440 464 552 579 580 584 589 594 596 613 621 624 625 628 62X 633 638 63X 652 657 65X 661 662 671 675 678 681 688 699 702 703 706 740 743 746 759 790 79Y BK KF KP KQ KT KW LA MA ME ML MM QT RE RR RX UJ
A5B 211 215 21Y 244 246 24Y 381 38Y 390 426 42Y 480 482 484 48Y 510 513 51Y 541 543 544 54Y 565 566 56Y 58Y 640 64Y 650 657 65Y 674 67Y 77Y

(19) THE PATENT OFFICE LONDON

...GORY, WILLIAM KINGSTON
... SEALE

ERRATA

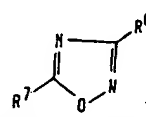
SPECIFICATION No. 1,397,073

Page 1, line 28, *for* hydrogen *read* hydroxy
Page 16, line 13, *delete* whole line *insert* or substituted by one or more C_{1-6} alkyl, C_{1-6}
Page 16, line 60, *for* diethyl- *read* dimethyl-
Page 16, line 68, *for* Piperidinocarbamoyl *read* Piperidinocarbonyl
Page 17, line 26, *for* amidomixe *read* amidoxime
Page 17, line 100, *for* arlkylthio *read* alkylthio

THE PATENT OFFICE
2nd July, 1976

substitute...

In one aspect the invention p... 1,2,4 - oxadiazole compounds of the general formula



I

where R^6 represents R, where R represents a hydrogen atom or an aliphatic cycloaliphatic, araliphatic, aryl or heterocyclic group; or a carbamoyl group of the formula —$CONR^1R^2$ where R^1 and R^2, which may be the same or different, represent hydrogen atoms, alkyl, alkenyl or alkynyl groups (or such groups substituted by a hydrogen group) cycloaliphatic, araliphatic or aryl groups or, together with the intervening N, represent a hertocyclic ring; and R^7 represents R, where R is as de-

...

amino, cyano, thiocyanate ... halogen atoms, for example, a tolyl, *p*-methoxyphenyl, *p*-nitrophenyl, *p*-chlorophenyl, *p*-methylthiostyryl, *p*-methylsulphinylstyryl or *p*-methoxystyryl group. The acyl portions of the acylamino may for example be straight or branched C_{1-6} alkanoyl groups. When an amino ring substituent is present the compounds may form salts e.g. with strong acids such as hydrochloric or nitric acid. Where R represents an aliphatic group this may for example be an optionally substituted alkyl, alkenyl or alkynyl group such as a methyl or ethyl group, an alkyl group, an ethynyl group or a propargyl group, which may carry heterocyclic groups as substituents e.g. 5- or 6-membered groups such

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A5B 211 215 21Y 244 246 24Y 381 38Y 390 426 42Y 480 482 484 48Y 510 513 51Y 541 543 544 54Y 565 566 56Y 58Y 640 64Y 650 657 65Y 674 67Y 77Y

(72) Inventors GORDON IAN GREGORY, WILLIAM KINGSTON WARBURTON and PETER WILLIAM SEALE

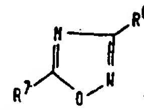
(54) 1,2,4-OXADIAZOLES

(71) We, GLAXO LABORATORIES LIMITED, a British Company of Greenford, Middlesex, England, do hereby declare the invention for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to new oxadiazole derivatives, processes for the preparation thereof and pharmaceutical compositions containing the same.

We have found that interesting physiological activity, particularly antimicrobial activity, including antiviral, antiparasitic and antibacterial activity, is shown by a group of 3 and/or 5-substituted 1,2,4 - oxadiazole compounds.

In one aspect the invention provides novel 1,2,4 - oxadiazole compounds of the general formula



I

where R^6 represents R, where R represents a hydrogen atom or an aliphatic cycloaliphatic, araliphatic, aryl or heterocyclic group; or a carbamoyl group of the formula —$CONR^1R^2$ where R^1 and R^2, which may be the same or different, represent hydrogen atoms, alkyl, alkenyl or alkynyl groups (or such groups substituted by a hydrogen group) cycloaliphatic, araliphatic or aryl groups or, together with the intervening N, represent a hertocyclic ring; and R^7 represents R, where R is as defined above or a carbamoyl group of the formula —$CONR^3R^4$, where R^3 and R^4 are as defined for R^1 and R^2; provided that at least one of R^6 and R^7 is an N- substituted carbamoyl group.

Thus, for example, R may represent an aryl group which is preferably mono- or bi-cyclic, such as a phenyl, naphthyl or diphenylyl group; or an araliphatic group such as an aralkyl, aralkenyl or aralkynyl group e.g. a benzyl, phenethyl, phenylethynyl or styryl group. R may alternatively represent a heterocyclic group, e.g. a 5- or 6-membered group such as a furyl, thienyl or pyridyl group. Such aryl, araliphatic and heterocyclic groups may carry one or more ring substituents such as C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkylthio, C_{1-6} alkylsulphinyl, lower alkylsulphonyl, amino, acylamino, cyano, thiocyanato or nitro groups or halogen atoms, for example, a tolyl, *p*-methoxyphenyl, *p*-nitrophenyl, *p*-chlorophenyl, *p*-methylthiostyryl, *p*-methylsulphinylstyryl or *p*-methoxystyryl group. The acyl portions of the acylamino may for example be straight or branched C_{1-6} alkanoyl groups. When an amino ring substituent is present the compounds may form salts e.g. with strong acids such as hydrochloric or nitric acid. Where R represents an aliphatic group this may for example be an optionally substituted alkyl, alkenyl or alkynyl group such as a methyl or ethyl group, an alkyl group, an ethynyl group or a propargyl group, which may carry heterocyclic groups as substituents e.g. 5- or 6-membered groups such

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as furyl, thienyl or pyridyl groups which may themselves carry substituents.

When R is an aliphatic group it is preferably saturated. Where R is a heterocyclic group or carries a heterocyclic substituent, the hetero atom(s) is preferably S and/or N, and the group is preferably not a nitrofuryl group.

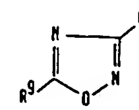
Where R is a cycloaliphatic group this may for example be a cycloalkyl group having 3-10 carbon atoms, e.g. a cyclohexyl group.

R^1, R^2, R^3 and R^4 may, for example, represent alkyl, alkenyl or alkynyl groups which may be substituted by hydroxy groups, especially C_{1-6} alkyl groups such as methyl, ethyl, propyl, *n*-butyl, *t*-butyl or 2-hydroxyethyl groups, alkenyl groups such as allyl groups or alkynyl groups such as a propargyl group; aryl groups especially monocyclic aryl groups such as phenyl groups, which may carry one or more alkyl or alkoxy substituents; aralkyl, aralkenyl, or aralkynyl groups especially monocyclic groups such as benzyl groups or cycloaliphatic groups especially monocyclic cycloalkyl groups such as cyclohexyl groups or caged cycloalkyl groups such as adamantyl groups. R^1 and R^2 or R^3 and R^4 may together with intervening N represent a substituted or unsubstituted nitrogen-containing heterocyclic group, which may contain a further hetero atom such as oxygen or nitrogen, e.g. a piperidino, morpholino, pyrrolidin - 1 - yl, piperazin - 1 -yl, 4 - (C_{1-6}) - alkylpiperazin - 1 - yl or 3 - azabicyclo - (3,2,2) - nonan - 3 - yl group. These heterocyclic groups may be substituted e.g. by the substituents described above for heterocyclic R groups.

In general each of the substituents R, R^1, R^2, R^3 and R^4 preferably has less than 20 carbon atoms; aliphatic groups preferably have up to 6 carbon atoms and alkyl, alkenyl and alkynyl portions of aralkyl, aralkenyl or aralkynyl groups preferably have up to 6 carbon atoms. Heterocyclic groups preferably have 5-10 ring members. Cycloalkyl groups preferably have 3—10, especially 3—7, carbon atoms.

Particularly preferred, by virtue of their physiological activity, are those compounds of the general formula I in which R represents an aryl group, especially a bicyclic and/or substituted aryl group, or an araliphatic group, which may also be substituted. The preferred R groups thus possess at least 7 carbon atoms. Preferred examples of substituents which may be present on aryl or araliphatic groups are alkyl (e.g. C_{1-6} alkyl), alkoxy (e.g. C_{1-6} alkoxy), alkylsulphinyl or alkylthio (e.g. C_{1-6} alkyl - sulphinyl or -thio), or nitro groups, and halogen atoms. Examples of such R groups are a tolyl, α-naphthyl, biphenylyl, *p*-methoxyphenyl, *p*-chlorophenyl, *p*-methylsulphinylstyryl or p-methylthiostyryl group, or a hydrogen atom. Carbamoyl groups of particular interest are those in which R^1, R^2, R^3 or R^4 represent an adamantyl group, or wherein R^1 and R^2 or R^3 and R^4 are both methyl, ethyl or *n*-propyl groups or, together with the intervening nitrogen atom, piperidino groups.

The compounds of formula I may be prepared by any conventional method, in particular by reaction of a compound of the general formula



II

(where R^8 and R^9, which may be the same or different, represent R as defined above, a group of the formula —$CONR^1R^2$ or —$CONR^3R^4$ as defined above or a carboxylic acid group or a reactive derivative thereof, provided that at least one of R^8 and R^9 represents a carboxylic acid group or a reactive derivative thereof) with a nitrogen base of the formula R^1R^2NH or R^3R^4NH (where R^1, R^2, R^3 and R^4 are as defined above) or, where a carboxylic acid of formula II is used, with an isocyanate of the formula R^1NCO or R^3NCO.

The reactive derivative may be, for example, an ester or an acid halide, e.g. choride, symmetrical or mixed anhydride or azide. The reactive derivatives are most conveniently the alkyl esters having 1—6 carbon atoms in the alkoxy moiety, e.g. the methyl or ethyl ester; araliphatic esters e.g. the benzyl ester; or aryl esters, e.g. *p*-nitrophenyl or *p*-chlorophenyl esters.

Where the compound of formula II is base-sensitive, e.g. when R^8 or R^9 is hydrogen, it is preferred to use an acid azide or halide, e.g. chloride, as reactive derivative. Such acid chlorides or azides may conveniently be prepared from the corresponding esters via the hydrazides. Where the reactive derivative is an ester, this is conveniently reacted with an excess of the nitrogen base either alone or in an inert solvent such as an alcohol, e.g. ethanol or methanol, a cyclic ether such as dioxan, a hydrocarbon solvent, such as toluene or a halogenated hydrocarbon solvent such as chloroform. The reaction is preferably effected at the reflux temperature of the system.

Reaction of the acid azide or halide is desirably effected in an inert solvent, e.g. a halogenated hydrocarbon solvent such as chloroform or an ester such as ethyl acetate, at ambient temperature. Where using an acid halide, an acid-binding agent is preferably present, e.g. pyridine, propylene oxide or triethylamine.

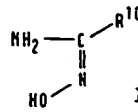
The amide formation can also be effected by reacting a carboxylic acid of formula II with the nitrogen base in the presence of a water-abstracting agent e.g. a diimide such as dicyclohexylcarbonyldiimide or carbonyldiimidazole; or alternatively with an isocyanate R^1NCO or R^3NCO giving a product in which

R^6 and/or R^7 represents —$CONHR^1$ or —$CONIR^3$ respectively.

The 1,2,4-oxadiazole ring system itself can be synthesised using any convenient method.

In particular, the compounds of formula II and certain products of formula I can be prepared from correspondingly substituted amidoximes employing 0-acylation and subsequent cyclisation, for example, using acid halides, anhydrides, azides, amides, esters or orthoesters. The acylation may be carried out where necessary in the presence of an acid binding agent such as pyridine, propylene oxide or triethylamine.

In one embodiment of this method, an amidoxime of the formula

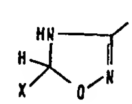

III

(where R^{10} represents R as defined above) is reacted with an oxalic acid derivative of the formula HalCOX where Hal represents a halogen atom, especially chlorine, and X a group —$CONR^3R^4$ or an esterified carboxylic acid group, as described in relation to R^8 and R^9, for example a lower (C_{1-6}) alkoxycarbonyl group, e.g. an ethoxycarbonyl group, to yield either (a) a product of the formula I in which R^6 represents R and R^7 represents a group of the formula $CONR^3R^4$ or (b) an intermediate of the formula II in which R^8 represents R and R^9 represents an esterfied carboxylic acid group.

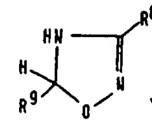
In another embodiment of the method an amidoxime of the formula III, where R^{10} represents an esterified carboxylic acid group, is reacted with the derivative of formula HalCOX as defined above to yield an ester of the formula II in which R^8 represents an esterified carboxylic acid group and R^9 represents an esterified carboxylic acid group or a group of the formula —$CONR^3R^4$. The reaction is advantageously carried out in the presence of an acid binding agent, such as pyridine, propylene oxide or triethylamine.

In a further embodiment an amidoxime of the formula III in which R^{10} represents an esterified carboxylic acid group is reacted with an acid halide of the carboxylic acid RCO_2H where R is as defined above yielding an ester of the formula II where R^8 represents an esterified carboxylic acid group and R^9 represents R as defined above. The reaction is advantageously carried out in the presence of an acid binding agent, such as pyridine propylene oxide or triethylamine.

Alternatively the amidoxime of formula III where R^{10} represents R, an esterified carboxylic acid group or a group —$CONR^1R^2$ is reacted with a glyoxylic acid derivative of the formula HCO X where X is as defined above to yield an oxadiazoline of formula


IV

which may be oxidised to give the corresponding oxadiazole of formula II, or where X and/or R^{10} represents an esterified carboxylic acid group, may be reacted with an amine HNR^3R^4 to give an oxadiazoline of formula


V

where R^8 represents R as defined above or a group —$CONR^1R^2$ and R^9 represents a group —$CONR^3R^4$ as defined above. Where R^{10} and X both represent an esterified carboxylic acid group, R^8 in the product formed of formula V represents a group $CONR^1R^2$ where R^1 and R^2 are identical to R^3 and R^4 in R^9. These oxadiazolines (and those wherein R^9 represents R) can be oxidised to yield a product of formula I and are themselves of interest as intermediates and accordingly form a further feature of the present invention.

Compounds of the formula II (in which R^9 represents a hydrogen atom and R^8 represents an esterified carboxylic acid group) or compounds of formula I (in which R^7 represents a hydrogen atom and R^6 represents a group —$CONR^12^2$) may be prepared by reacting an amidoxime of formula III, where R^{10} represents an esterified carboxyl group or a group —$CONR^1R^2$, with an orthoformate, e.g. triethyl or trimethyl orthoformate in the presence of a Lewis acid such as boron trifluoride or its etherate; or with formyl fluoride, conveniently at reduced temperature e.g. −78° to ambient temperature, in an inert solvent. Alternatively, this reaction may be carried out with a Meerwein reagent (e.g. a dialkyl acetal of dimethylformamide) or the Wilsmeier-Haack reagent (phosphorus oxychloride and dimethylformamide).

In general, the preparation of a compound of formula I or formula II, whether substituted or unsubstituted at the 5 - position, from an amidoxime of formula III may be effected in an inert solvent. Alternatively an excess of the reagent may be used, for example when using an orthoformate as reagent. Where acid halides are used, halogenated hydrocarbon solvents such as chloroform are particularly suitable and an acid-binding agent is preferably present, e.g. pyridine, propylene oxide or triethylamine.

The reaction with the amidoxime is conveniently effected at an ambient temperature or a moderately elevated temperature for example the reflux temperature of the system.

The oxidation of an oxadiazoline to an oxadiazole is conveniently effected, for example,

using manganese dioxide, potassium or sodium permanganate, sodium nitrite, ferric chloride, palladised charcoal and air, chloranil or related quinones. This reaction is conveniently effected in a solvent the nature of which will depend upon the oxidising agent used. Suitable solvents include for example methanol, chloroform and ethyl acetate.

The temperature at which the oxidation is carried out will also depend on the oxidising agent used but will generally be between 0 to 100° C.

It will be appreciated that for compounds of the formula I in which R represents an aryl or araliphatic group carrying a substituent, it may be preferable first to prepare a compound of formula I having a different substituent by a method as set forth above, which substituent is thereafter converted into the desired substituent. Thus for example, if it is desired that R be an aminophenyl or a cyanophenyl group, it is convenient first to prepare a compound in which R is nitrophenyl, the nitro group being then reduced to an amino group, which latter may then, if desired, be converted to, for example, a cyano group or halogen atom e.g. by a Sandmeyer reaction. Furthermore compounds bearing alkylsulphinyl and alkylsulphonyl groups in the group R may advantageously be prepared from the corresponding alkyl-thio compounds by oxidation, for example using peracetic acid or aqueous hydrogen peroxide; where it is desired to form an alkylsulphinyl group, in general approximately one equivalent of oxidising agent will be used.

It should further be noted that the oxidation of such substituents in the group R in a corresponding oxadiazoline ring can yield the oxadiazole product of formula I and this constitutes a variation of the oxidation method described above.

As stated above, interesting antiviral activity has been shown in the group of compounds in accordance with the invention, principally against Rhinovirus strains, particularly Rhinovirus M1, and Rhinovirus H9. 3 - Adamantylcarbamoyl - 1,2,4 - oxidiazole has shown noteworthy activity against Influenza A2 and Herpes simplex viruses.

The following Table I lists a number of compounds identified with respect to formula I having especially high activity against Rhinovirus, especially the strains M1 and H9 which are indicated as RM1 and RH9:

TABLE I

R^6	R^7	Rhinovirus strains
$C_{10}H_7(\alpha)$	Et_2NCO	RM1
p-MeO-phenyl	Et_2NCO	RM1
$CONMe_2$	*p*-Cl-phenyl	RM1
$CONMe_2$	$C_{10}H_7(\alpha)$	RM1
trans-*p*-MeS-styryl	Me_2NCO	RM1, RH9
p-MeO-phenyl	piperidinocarbonyl	RM1, RH9
$C_{10}H_7(\alpha)$	piperidinocarbonyl	RM1, RH9
p-MeO-phenyl	Me_2NCO	RM1
$C_{10}H_7(\alpha)$	Me_2NCO	RM1, RH9
$C_{10}H_7(\alpha)$	n.Pr_2NCO	RH9
$CONMe_2$	*p*-tolyl	RM1
trans-*p*-MeS-styryl	Et_2NCO	RM1, RH9
Biphenylyl	Et_2NCO	RM1, RH9

The anti-viral compounds may be formulated for administration in conjunction, if desired, with one or more pharmaceutical or veterinary carriers or excipients suitable, for example for oral, topical, rectal, intravaginal or parenteral administration. The pharmaceutical or veterinary composition so formed may include other therapeutically effective com-

pounds, for example anti-inflammatory agents such as steroids, e.g. betamethasone - 21 - phosphate, or antibiotics such as tetracycline.

5 - Diethylcarbamoyl - 3α - naphthyl - 1,2,4 - oxadiazole and 3 - biphenylyl - 5-diethylcarbamoyl - 1,2,4 - oxidiazole have been found to be particularly suitable for formulation for topical administration.

Solid preparations for oral consumption are usually present in unit dose form and include for instance, tablets, capsules, lozenges, chewing gum and medicated sweets.

Each dosage unit preferably contains 0.05 to 4 g of active antiviral material, advantageously 0.1 to 1.0 g. The material may be administered, for example, 1 to 3 times per day but the total daily dose should be in the range 0.1 to 7 g. It will be seen from the foreging table that the compounds are of particular interest in combatting Rhinovirus infections.

Conventional carriers for such preparations may be sugars, starches, sugar alcohols, gelatin, chicle gum and cocoa butter, together with other compounding agents required such as binders, lubricants, stabilisers, coatings, flavourings and colourings. The compositions may also take the form of liquid oral preparations for ingestion such as solutions, suspensions, syrups, elixirs, emulsions and granules for reconstitution before use, which may contain suspending, emulsifying, stabilising and preserving agents and may also contain acceptable sweetening, flavouring or colouring agents. The compounds may be prepared for local application to the mucous membranes of the nose and throat and may take the form of liquid sprays or powder insufflations, nasal drops or ointments, throat paints, gargles or similar preparations. Topical formulations for the treatment of eyes and ears and external applications may be prepared in oily, aqueous or powdered media in the form of conventional ophthalmic preparations and collyria, skin paints, lotions, creams, ointments, dusting powders, medicated dressings, eye drops and lotions. Aerosol forms of the preparations for local application may also be advantageous. Suppositories and pressaries may contain a conventional base e.g. oil of theobroma, polyglycols, glyco-gelatin bases together with surface active agents if required. The injectable preparations may take the form of aqueous or oily solutions, emulsions, suspensions or solids for reconstitution before use. Suitable vehicles include, for example, sterile, pyrogen-free water, parenterally acceptable oils, oily esters or other non-aqueous media such as propylene glycol if desired containing suspending, dispersing, stabilising, preserving, solubilising, emulsifying or buffering agents.

As stated above, antiparasitic activity has also been shown in the group of compounds in accordance with the invention, particularly against *Entamoeba histolytica*. 5 - Diethylcarbamoyl - 3 - *p* - methyl - sulphinylstyryl - 1,2,4 - oxadiazole has been shown to be highly active against this parasite. Other compounds which have shown activity against this parasite are: 5 - Dimethylcarbamoyl - 3-methyl - 1,2,4 - oxadiazole; 5 - methylcarbamoyl - 3 - methyl - 1,2,4 - oxadiazole; 5-diethylcarbamoyl - 3 -*p* - methoxyphenyl - 1,2,4 - oxadiazole; and trans - 5 - diethylcarbamoyl - 3 - *p* - methylthiostyryl - 1,2,4 - oxadiazole.

Activity has also been shown against the Helminth *Namatospiroides dubius*, particularly by 5 - dimethylcarbamoyl - 3 - phenyl - 1,2,4-oxadiazole.

Trans - 5 - diethylcarbamoyl - 3 - (5 - nitrofuryl - 2 - ylvinyl) - 1,2,4 1 oxadiazole has also shown activity against S. aureus, E. coli, B.C.G. S. typhinurium. It has also been found to be active against M. canis.

The compounds may be formulated for antiparasitic and antibacterial administration by the methods described above. When presented in unit dose form, each dosage unit may generally contain 2—500 mg, preferably 2—250 mg, of the active ingredient. The material may be administered at a daily dose of 0.5 to 100 mg/kg, preferably 1—60 mg/kg, and most conveniently 1—20 mg/kg body weight.

The invention is further illustrated by the following examples. The preparation of certain novel starting materials is given as a series of Preparations. The products of these Preparations are then used in the Examples. Temperatures are in °C.

PREPARATION 1.

5 - Ethoxycarbonyl - 3 - methyl - 1,2,4 - oxadiazole:—

To a stirred suspension of acetamidoxime (3.2g.) in ethanol-free chloroform (25 ml.) containing pyridine (10 ml.) was added ethyl oxalyl chloride (8.7 g.) with cooling. The resulting solution was heated under reflux for one hour and then cooled, shaken with 2-N - hydrochloric acid (30 ml), and the with water (25 ml.), dried, and evaporated to dryness to give a yellow oil.

Distillation under vacuum gave title compound (4.36 g.) b.p. 57.61° at 0.4 mm $\nu_{max.}$ ($CHBr_3$) 1750 $cm.^{-1}$ ($—CO_2Et$).

PREPARATION 2.

5 - Ethoxycarbonyl - 3 - α - naphthyl - 1,2,4-oxadiazole.

A solution of ethoxalyl chloride (24 ml.) in ethanol-free chloroform (25 ml.) was added dropwise with cooling during 30 min. to a suspension of α - naphthylcarbonamidoxime (34.78g.) in ethanol-free chloroform (120 ml.) containing pyridine (30 ml.). The mixture was heated under reflux for 1 hr. and cooled. The solution was washed with 2N - hydrochloric acid and water and then dried. The chloroform solution was evaporated to dry-

ness under reduced pressure leaving a pale yellow solid which was stirred with aqueous methanol to give title compound (31.8 g), m.p. 68.70°, $\lambda_{max.}$ (EtOH) 302 nm (ϵ 8,420). Similarly was prepared:—

PREPARATION 3.

3 - Biphenylyl - 5 - ethoxycarbonyl - 1,2,4 - oxadiazole in 98.6% yield, m.p. 81.82° (MeOH), $\lambda_{max.}$ (EtOH) 272 nm (ϵ 26,400), $\nu_{max.}$ ($CHBr_3$) 1750 cm.$^{-1}$ (CO_2Et).

PREPARATION 4.

5 - Ethoxylcarbonyl - 3 -trans - p - methylthiostyryl - 1,2,4 - oxadiazole.

Ethoxalyl chloride (8.7g.) in ethanol-free chloroform (50 ml.) was added during 1 hr. to a stirred suspension of *p*-methylthiocinnamamidoxime (11.6g.) in chloroform (600 ml.) and pyridine (5.15 ml.) at −3°. After 16 hr. at −20° the solution was filtered and refluxed for 1 hr. with azeotropic removal of water. The solution was cooled and washed successively with 2N - hydrochloric acid, sodium hydrogen carbonate solution and water. The solution was dried and evaporated. The residue was crystallised from aqueous acetone (charcoal) to give the title compound (12.7 g.), m.p. 88—89°, $\lambda_{max.}$ (TtOH) 237, 326 nm (ϵ12,400 and 29,500), $\nu_{max.}$ ($CHBr_3$) 1752, 1648 and 973 cm.$^{-1}$.

PREPARATION 5.

5 - Ethoxcarbonyl - 3 - p - methoxyphenyl - 1,2,4 - oxadiazole.

Ethoxalyl chloride (11 ml.) in ethanol-free chloroform (5.6 ml.) was added at 0° over a period of 45 min. to a stirred solution of *p*-methoxybenzamidoxime (13.45g.) in chloroform (73 ml.) containing pyridine (6.5 ml.) Stirring was continued at room temperature for a further 2.5 hr. Chloroform was added and the solution was washed successively with 2N - hydrochloric acid, water, sodium hydrogen carbonate, and water. Evaporation left a residue which was chromatographed on silica (1 kg.) in benzene-ethyl acetate (9:1 v/v) to give the oxadiazole as an oil (11.73g.) which slowly crystallised. Recrystallisation from aqueous acetone gave the title compound, m.p. 59—60°, $\lambda_{max.}$ (EtOH) 252 nm (ϵ 21,200).

PREPARATION 6.

3 - trans - p - Chlorostyryl - 5 - ethoxycarbonyl - 1,2,4 - oxadiazole.

p - Chlorocinnamamidoxime (anhydrous, 25.74g.) was dissolved in chloroform (300 ml.) containing pyridine (10.34g.). Eethyl oxalyl chloride (16.5g.) in chloroform (15 ml.) was added dropwise, with stirring. Stirring was continued for 1 hr., then the mixture was filtered and the filtrate was evaporated to dryness under reduced pressure. The residue was recrystallised from aqueous ethanol to give title compound (9.76 g.) m.p. 94—95°. $\lambda_{max.}$ (EtOH) 228, 285, nm. (ϵ 12,990, 31,450) $\nu_{max.}$ ($CHBr_3$) 975 cm.$^{-1}$ (trans—CH=CH).

PREPARATION 7.

3,5 - Bis - ethoxycarbonyl - 1,2,4 - oxadiazole.

Ethyl oxalyl chloride (10 ml.) was added dropwise, with cooling, to a solution of ethoxycarbonyl - formamidoxime (10g.) in ethanol-free chloroform (100 ml.) containing pyridine (10 ml.). The mixture was heated under reflux for 1 hr., cooled and washed with 2N - hydrochloric acid (50 ml.) and water (50 ml.) and dried. Evaporation gave title compound (6.5 g.), n_D^{21} 1.4571.

PREPARATION 8.

5 - Hydrazinocarbonyl - 3 - α - naphthyl - 1,2,4 - oxadiazole:—

5 - Ethoxycarbonyl - 3 - α - naphthyl - 1,2,4 - oxadiazole (10.0g.) was dissolved in methanol (150 ml.) and hydrazine hydrate (10.0g.) added dropwise with cooling. The mixture was stirred for fifteen minutes and the crystalline precipitate was filtered off, washed with methanol (10 ml.), and dried to give title compound (7.08 g), m.p. 211—212° (decomp.) λ_{max} (EtOH) 302 nm (ϵ 10,100) $\nu_{max.}$ (Nujol) 1680 cm.$^{-1}$ (—CONH—).

Similarly were prepared:—

PREPARATION 9.

5 - Hydrazinocarbonyl - 3 - methyl - 1,2,4 - oxadiazole in 54.7% yield, m.p. 150—151°, $\nu_{max.}$ (Nujol) 1672 cm.$^{-1}$ (—CONH—).

PREPARATION 10.

trans - *5 - Hydrazinocarbonyl - 3 - p - methylthiostyryl - 1,2,4 - oxadiazole* in 92.4% yield, m.p. 207° (decomp.) $\lambda_{max.}$ (EtOH) 238, 326 nm (ϵ 15,300, 31,000) $\nu_{max.}$ (Nujol) 1670 cm.$^{-1}$ (—CONH—) τ (d^6 DMSO) 7.47 (CH_3S—) 2.73 (doublet, J 16 Hz.) and 2.24 (doublet, J 16 Hz.) —CH=CH— (trans).

PREPARATION 11.

5 - Azidocarbonyl - 3 - α - naphthyl - 1,2,4- oxadiazole:—

5 - Hydrazinocarbonyl - 3 - α - naphthyl- 1,2,4 - oxadiazole (6.47g.) was dissolved in acetic acid (125 ml.) and *2N* - hydrochloric acid (75 ml.). A solution of sodium nitrite (2.0g) in water (6 ml.) was added at 0° with stirring. After fifteen minutes the precipitate was filtered off and dissolved in chloroform. The chloroform solution was washed with water and dried ($MgSO_4$). Evaporation to dryness gave title compound (5.82 g.), m.p. 114° (decomp.), $\lambda_{max.}$ (EtOH) 300 nm. (ϵ 8,250), $\nu_{max.}$ ($CHBr_3$) 1710 (C=O), 2150 and 2190 cm.$^{-1}$ (N_3).

Similarly were prepared:—

PREPARATION 12.

trans - *5 - Azidocarbonyl - 3 - p - methylthiostyryl - 1,2,4 - oxadiazole* in 73.7% yield, m.p. 125° (decomp.) $\lambda_{max.}$ (EtOH) 237, 325 nm. (ϵ 12,400, 24,300), $\nu_{max.}$ ($CHBr_3$) 1715 (C=O), 2160 and 2202 cm.$^{-1}$ (N_3), τ (d_6—DMSO) values include 2.21 (doublet J 16 Hz) and 2.68 (doublet J 16 Hz, trans CH=CH).

PREPARATION 13.

5 - Azidocarbonyl - 3 - methyl - 1,2,4 - oxadiazole in 33.4% yield, m.p. 71—72°, $\nu_{max.}$ ($CHBr_3$) 1710 (C=O), 2150 and 2192 cm.$^{-1}$ (N_3).

PREPARATION 14.

3 - Ethoxycarbonyl - 5 - p - tolyl - 1,2,4 - oxadiazole.

Ethoxycarbonylformamidoxime (46.0g) was stirred in chloroform (450 ml.) and pyridine (32.5 ml.) and a solution of *p*-tolyl chloride (54g.) in chloroform (50 ml.) was added during 1 hr. and stirring was continued for a further 1 hr. The solid that separated was filtered off and washed with water to give the O-acylated amidoxime (63.5g., 72%), m.p. 188—190°. Parts of this product (5.0g.) was heated under reflux in xylene (100 ml.) for 4 hr. with azeotropic removal of water; the xylene was then removed under reduced pressure. The residue was recrystallised from aqueous methanol to give the title compound (4.4g.) m.p. 76—77°, $\lambda_{max.}$ (EtOH) 263 nm. (ϵ 19,620) ν_{max} ($CHBr_3$) 1750, 1210 cm.$^{-1}$ (CO_2Et).

PREPARATION 15.

5 - p - Chlorophenyl - 3 - ethoxycarbonyl - 1.2.4 - oxadiazole.

p-Chlorobenzoyl chloride (9.5g.) in chloroform (20 ml.) was added dropwise to a stirred solution of ethoxycarbonyl - formamidoxime (7.21g.) in chloroform (60 ml.) and pyridine (18 ml.). After 1 hr. the solid (12.32g.) was filtered off and washed with chloroform. Some of this solid (10.0g.) was heated under reflux in xylene (250 ml.) for 20 hr., with azeotropic removal of water. The xylene was removed under reduced pressure, and the residue was recrystallised from ethanol to give title compound (8.11 g.), m.p. 93.5°, λ_{max} (EtOH) 261—262 nm. (ϵ 2,540), $\nu_{max.}$ ($CHBr_3$) 1745 and 1210 cm.$^{-1}$ (CO_2ET).

The following compounds were similarly prepared:

PREPARATION 16.

3 - Ethoxycarbonyl - 5 - p - nitrophenyl - 1,2,4 - oxadiazole in 88% yield, m.p. 144—145°, $\lambda_{max.}$ (EtOH) 274 nm (ϵ 21,200) $\nu_{max.}$ ($CHBr_3$) 1750 and 1218 (CO_2Et), 1536 and 1350 cm^{-1} (NO_2).

PREPARATION 17.

3 - Ethoxycarbonyl - 5 - (2 - thienyl) -1,2,4 - oxadiazole in 43% yield, m.p. 76°, $\lambda_{max.}$ (EtOH) 263—264, 289 nm, (ϵ10,960, 16,280), $\nu_{max.}$ ($CHBr_3$) 1210 and 1745 cm.$^{-1}$ (CO_2Et).

PREPARATION 18.

3 - Ethoxycarbonyl - 1,2,4 - oxadiazole.

Ethoxycarbonylformamidoxime (39.6g., 300 mmole) was added to triethyl orthoformate (180 ml.) containing boron trifluoride etherate (0.9 ml.), and the solution was heated under reflux for 1 hr., then cooled and filtered. The filtrate was evaporated to dryness under reduced pressure and the residue, dissolved in chloroform was washed with 2*N*-hydrochloric acid, then with saturated sodium hydrogen carbonate solution and dried ($MgSO_4$). Removal of the solvent left an oil (37.2g.) which partially crystallised. The residual oil was sucked off, leaving the oxadiazole, (33.94g), m.p. 41—43°, b.p. 80—90° (bath)/0.6 nm.

PREPARATION 19.

3 - Hydrazinocarbonyl - 1,2,4 - oxadiazole.

Hydrazine hydrate (98%, 3.15 ml.) was added at <15° in 3 portions during 20 min. to a stirred solution of 3 - ethoxycarbonyl - 1,2,4 - oxadiazole (5.96 g.) in dry ethanol (29 ml.). The mixture was stirred for 50 min. at 0° and then filtered, to give title compound 5.26 g., m.p. 112° (decomp.) $\lambda_{max.}$ 242—243 nm (ϵ 3,950).

PREPARATION 20.

3 - Azidocarbonyl - 1,2,4 - oxadiazole.

Sodium nitrite (2.70g.) in water (7.5 ml.) was added, at 0°, with stirring, during 40 min., to a solution of 3 - hydrazidocarbonyl - 1,2,4-oxadiazole (4.48 g.) in 2N-hydrochloric acid (50 ml.) and glacial acetic acid (20 ml.). After 1 hr., water was added and the product was extracted into chloroform Evaporation of the solvent and removal of residual acetic acid under vacuum gave the azide, (3.17 g), m.p. 89—90°, $\lambda_{max.}$ (EtOH) 241 nm (ϵ 4,580).

PREPARATION 21.

3 - Chlorocarbonyl - 1,2,4 - oxadiazole.

Dry hydrogen chloride was passed for 2 hr. through a solution of 3 - hydrazidocarbonyl-1,2,4 - oxadiazole (11.96g., 93.7 mmole) in dry methanol (630 ml.), then the solution was evaporated to dryness. Dry nitromethane (30 ml.) was added and the evaporation was repeated. The residue was dissolved in nitromethane (200 ml.) and hydrogen chloride was again passed into the solution for 45 min. Chlorine was then passed in for 1 hr., when the evolution of nitrogen ceased. The residual chlorine was removed by the passage of nitrogen, the suspension was filtered, and the fil-

trate was evaporated to give the crude acid chloride, 10.2 g. Distillation gave title compound b.p. 47—47.5°/2.5 mm. $\nu_{max.}$ (CS_2) 1785 (COCl), 3130 cm.$^{-1}$ (CH).

PREPARATION 22.

5 - Ethoxycarbonyl - 3 - α - naphthyl - 1,2,4-oxadiazole.

α-Naphthylcarbonamidoxime (149.5g.) was suspended in dry ethyl acetate (510 ml.) and propylene oxide (153 ml.). A solution of ethyl oxalyl chloride (97 ml.) in dry ethyl acetate (100 ml.) was added to the stirred suspension at 0 to 5° during 1 hour. The solution was stirred at room temperature for 30 minutes and then heated under reflux for 2 hours. The cooled solution was washed with *2N*-sodium carbonate solution and water and dried over sodium sulphate. Removal of the solvent under reduced pressure gave a brown oil (237.9 g.) which was vigorously stirred with methanol-water (7:1, v/v) (131 ml.), and dried to give the ester 193.1 g., 89.7%), m.p. 72—73°.

PREPARATION 23.

5 - Ethoxycarbonyl - 3 - p - methoxystyryl - 1,2,4 - oxadiazole.

p-Methoxycinnamamidoxime (1.25 g.) was stirred in dry ethyl acetate (20 ml.) and propylene oxide (0.9 ml.) was added. A solution of ethyl oxalyl chloride (0.84 ml.) in ethyl acetate (5 ml.) was added dropwise, with stirring, during 30 minutes at 0—5°. The suspension was allowed to warm to 18° and was then heated under reflux for 90 minutes. The solution was cooled, washed with *2N*-sodium carbonate solution and with water, dried and treated with charcoal. Removal of the solvent and recrystallisation from methanol gave the oxadiazole (1.534 g., 86%), m.p. 115—116°, $\lambda_{max.}$ (EtOH) 225.5, 300 (infl.), and 308.5 nm (ε 14500, 26000 and 26600), $\nu_{max.}$ ($CHBr_3$) 820 (C_6H_4), 970 (*trans*—CH=CH), 1752 (C=O), cm.$^{-1}$.

PREPARATION 24.

trans - 5 - Ethoxycarbonyl - 3 -(5 - nitrofur - 2 - ylvinys) - 1,2,4 - oxadiazole.

trans - 5 - Nitrofur - 2 - ylacrylamidoxime (2.0 g.) was suspended in ethanol-free chloroform (40 ml.) containing pyridine (1.6 ml.). Ethoxalyl chloride (2.5 ml.) was added dropwise and the mixture was heated under reflux for 2 hours. After cooling the reaction mixture was poured into water (100 ml.) and extracted with chloroform (100 ml.). The dried (MgSO4) extract was evaporated to dryness and the residue was crystallised from methanol (90 ml.) to give the title compound (2.3 g., 80%), m.p. 138—139°, $\nu_{max.}$ ($CHBr_3$) 1755 (CO_2Et), 1508 and 1350 (NO_2), 959 cm.$^{-1}$ (trans CH=CH).

PREPARATION 25.

3 - Benzyl - 5 - ethoxycarbonyl - 1,2,4 - oxadiazole.

Ethoxalyl chloride (1.75 ml.) in dry ethyl acetate (10 ml.) was added at 0—5° during 10 minutes to a stirred solution of phenylacetamidoxime (1.5 g.) in ethyl acetate (10 ml.). After stirring at room temperature for 90 minutes the mixture was heated under reflux for 2½ hours. The solution was washed with 2N - sodium carbonate and water, dried and evaporated to give a yellow oil which was chromatographed on silica (100 g.). Elution with benzene-ethylacetate (3:1) gave the oxadiazole (2.25 g.) which was subsequently distilled, b.p. 170°—180° at 1.3 mm $\nu_{max.}$ ($CHBr_3$) 1750 cm.$^{-1}$ (ester).

EXAMPLE 1.

5 - Diethylcarbamoyl - 3 - α - naphthyl - 1,2,4-oxadiazole.

5 - Ethoxycarbonyl - 3 - α - naphthyl -1,2,4-oxadiazole (30.9g.) was heated under reflux in an excess of diethylamine (35.6g.) for 1.5 hr. The mixture was cooled and evaporated under reduced pressure to give a solid which was recrystallised from methanol yielding title compound (29.3 g.), m.p. 101.5—102.5°, $\lambda_{max.}$ (EtOH) 302 nm. (ε 9,700), $\nu_{max.}$ ($CHBr_3$) 1662 cm.$^{-1}$ ($CONEt_2$).

EXAMPLE 2.

trans - 5 - Dimethylcarbamoyl - 3 - p - methylthiostyryl - 1,2,4 - oxadiazole.

trans - 5 - Ethoxycarbonyl - 3 - *p* - methylthiostyryl - 1,2,4 - oxadiazole (600 mg.) was heated to reflux for 30 min. in an ethanolic solution of dimethylamine (10 ml.). The reaction mixture was evaporated to dryness and the solid residue was crystallised from methanol (8 ml.) to give title compound (544 mg.), m.p. 119—120°, $\lambda_{max.}$ (EtOH) 238, 315 (inflection), 327 nm. (ε 15,800; 26,000, 30,950) $\nu_{max.}$ ($CHBr_3$) 1668 (—$CONMe_2$) and 978 cm.$^{-1}$ (trans CH=CH).

EXAMPLE 3.

trans - 5 - Diethylcarbamoyl - 3 - p - methylthiostyryl - 1,2,4 - oxadiazole.

trans - 5 - Ethoxycarbonyl - 3 - *p* - methylthiostyryl - 1,2,4 - oxadiazole (13.3g.) was heated under reflux with a mixture of diethylamine (80 ml.) and methanol (20 ml.) for 1 hr. The cooled reaction mixture was evaporated and the residue was recrystallised from aqueous methanol to give the title amide (11.5 g.), m.p. 78—89°, $\lambda_{max.}$ (EtOH) 237, 311 (inflection), 326 nm (ε 16,100; 23,000; 32,000) $\nu_{max.}$ ($CHBr_3$) 1663 ($CONEt_2$) and 972 cm.$^{-1}$ (trans CH=CH).

EXAMPLE 4.

5 - Dimethylcarbamoyl - 3 - α - naphthyl - 1,2,4 - oxadiazole.

5 - Ethoxycarbonyl - 3 - α - naphthyl - 1,2,4-oxadiazole (618 mg.) was dissolved in an ethanolic solution of dimethylamine (10 ml., 33% v/v). After 1 hr. the solution was evaporated leaving a residue that was recrystallised from methanol (3.5 ml.) to give title compound (424 mg.,) m.p. 109—110°, $\lambda_{max.}$ (EtOH) 302.5 nm (ϵ 9,400) $\nu_{max.}$ ($CHBr_3$) 1660 cm.$^{-1}$ ($CONMe_2$).

EXAMPLE 5.

3 - Adamant - 1 - ylcarbamoyl - 1,2,4 - oxadiazole.

3 - Azidocarbonyl - 1,2,4 - oxadiazole (350 mg.) was added to a solution of 1 - aminoadamantane (378 mg.) in chloroform (15 ml.) and the mixture was stirred for 24 hr. The chloroform solution was evaporated to dryness under reduced pressure and the residue was recrystallised from aqueous methanol to give title compound (167 mg.), m.p. 141—142°, $\lambda_{max.}$ (EtOH) 230 nm (ϵ 3,910), $\nu_{max.}$ (Nujol) 3392 (—NH—) 1692 and 1515 cm^{-1} (CONH). Further examples provided in Table II were prepared by the following general methods:—

Method A.

The appropriate 3- or 5-alkoxycarbonyl - 1,2,4 - oxadiazole was treated with an excess of the primary or secondary amine (1—10 equivs.) at a suitable temperature, between ambient temperature and the boiling point. Excess amine was removed under reduced pressure and the product was recrystallised.

Method B.

Similar to Method A except that a solvent such as ethanol or methanol was used as diluent.

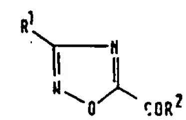
Method C.

The appropriate 3- or 5 - azidocarbonyl - 1,2,4 - oxadiazole was treated with the primary or secondary amine (1—2 equivs.) at room temperature in a suitable solvent (e.g. chloroform) and the product isolated by evaporation and recrystallisation.

Method D.

Similar to Method C except that the 3- or 5 - chlorocarbonyl - 1,2,4 - oxadiazole was used to acylate the amine.

Examples 6—40 refer to the formula



Examples 41—51 refer to the formula

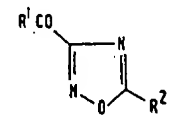


TABLE II

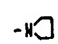
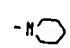
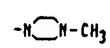
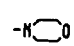
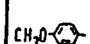
Example No.	R^1	R^2	Method	Cryst. Solvent	M.p. °C	λmax. nm. (EtOH)	ε	νmax. (-CON<) $cm.^{-1}$ ($CHBr_3$)	Yield %
6	Ph	$-N(CH_3)_2$	B(EtOH)	MeOH	79– 81°	244	7,300	1678(CS_2)	67
7	Ph	$-NHCH_3$	B(EtOH)	MeOH	114–115	–	–	1715(CS_2)	56
8	Ph	$-N(C_2H_5)_2$	A	petrol (40–60°)	45– 46	–	–	1660	71
9	Ph	$-NHC_2H_5$	A	EtOH/petrol (40–60°)	89– 90	–	–	1700	79
10	CH_3	$-N(CH_3)_2$	B(MeOH)	MeOH/petrol (60–80°)	35– 37	–	–	1660	70
11	Ph	–NHPh	C	MeOH/petrol (80–100°)	110–112	–	–	1710	72
12	Ph	$-N(CH_3)Ph$	C	,,	83– 85	–	–	1662	63
13	CH_3	$-NHCH_3$	B(MeOH)	benzene	99–101	–	–	1658	48
14	Ph		A	EtOH	138–140	231	18,000	1650	60
15	Ph		A	EtOH	66– 67.5	235	17,000	1660	47
16	Ph		A	Et_2O	81– 83	224	18,300	1655	49
17	Ph		A	EtOH	82– 83	235	15,300	1658	82
18		$-N(C_2H_5)_2$	A	EtOH	62– 63	256.5	19,360	1643	35

TABLE II (Continued)

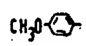
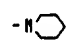
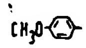
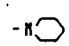
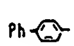
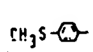
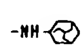
Example No.	R^1	R^2	Method	Cryst. Solvent	M.p. °C	λmax. nm. (EtOH)	ε	νmax. (–CON<) $cm.^{-1}$ ($CHBr_3$)	Yield %
19			A	$MeOH/H_2O$	78– 79	258	19,660	1656	43
20		$-N(CH_3)_2$	B(EtOH)	EtOH	123–124	256	19,600	1665	81
21	$\alpha-C_{10}H_7$		A	$MeOH/H_2O$	107–108	302.5	10,260	1655	55
22	$\alpha-C_{10}H_7$	$-N(CH_3)_2$	B(EtOH)	MeOH	109–110	302.5	9,370	1660	68
23	$\alpha-C_{10}H_7$	$-N(C_3H_7)_2$	A	MeOH	41.5–43	302.5	10,350	1658	52
24	$\alpha-C_{10}H_7$	$-N(CH_3)Ph$	C	MeOH	88– 89	293	8,900	1670	40
25	$\alpha-C_{10}H_7$	$-N(C_4H_9)_2$	C	–	oil	302	7,450	1650	78
26	$(C_2H_5)_2NCO-$	$-N(C_2H_5)_2$	A	MeOH	55– 56	235inf.	6,030	1660	55
27		$-N(C_2H_5)_2$	A	MeOH	81– 82	275.5	28,100	1660	72
28			C	EtOH	130–131	238 327	16,800 30,600	1700	71.5
29	$\alpha-C_{10}H_7$		C	$MeOH/H_2O$	64– 65	302	8,590	1696	81
30		$-NHC_4H_9$	A	MeOH	105–106	237 326	17,300 30,500	1692	57

TABLE II(Continued)

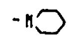
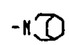
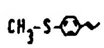
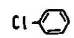
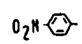
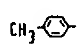
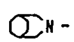
Example No.	R^1	R^2	Method	Cryst. Solvent	M.p. °C	λmax. nm. (EtOH)	ε	νmax. (–CON) cm.$^{-1}$ ($CHBr_3$)	Yield %
31		$-N(C_2H_5)_2$	A	MeOH	73– 74	221, 227, 285	18,700, 16,100, 31,900	1660	87
32			A	MeOH	115–116	220, 227.5	18,900, 15,400	1660	80
33	CH_3		C	–	86– 88	234	6,110	1700	65
34	$\alpha-C_{10}H_7$		C	MeOH	120–121	302	9,480	1662	59
35		$-NHC(CH_3)_3$	A	MeOH	113–114	235.5, 325	16,800, 30,400	1702	67
36	$\alpha-C_{10}H_7$	$-N(C_2H_5)_2$	A	MeOH	84– 85	226, 246, 322	38,900, 25,500, 15,300	1665	67
37	$\alpha-C_{10}H_7$	$-N(CH_2CH_2OH)_2$	B	MeOH	118–119	301.5	9,300	1662	66
38	$\alpha C_{10}H_7$		B	MeOH	119–120	302.5	8,810	1695	75
39	$\alpha C_{10}H_7$	$-NHCH_2CH=CH_2$	B	EtOH	105–106	302.5	8,700	1700	74
40	$PhCH-_2$	$-N(C_2H_5)_2$	A	–	Oil	253.5	2,200	1662	100
41	$(CH_3)_2N-$	CH_3	B(MeOH)	–	liquid	–	–	1660	48
42	CH_3NH-	CH_3	B(MeOH)	MeOH/petrol (40–60°)	109–110	–	–	1700	74

TABLE II (Continued)

Example No.	R^1	R^2	Method	Cryst. Solvent	M.p. °C	λmax. nm. (EtOH)	ε	νmax. (–CON<) $cm.^{-1}$ ($CHBr_3$)	Yield %
43	$(CH_3)_2N$–	Ph	C	$CHCl_3$/petrol (60–80°)	80– 81	–	–	1658	78
44	$(C_2H_5)_2N$–	Ph	A	–	liquid	–	–	1640	68
45		H	C, D	–	156–157	271.5	11,300	1710	77, 97
46	$(CH_3)_2N$–		B(MeOH)	MeOH/H_2O	97– 99	260	28,200	1650	65
47	$(CH_3)_2N$–	α–$C_{10}H_7$	B(MeOH)	MeOH/H_2O	109–110	239 312	27,600 17,000	1652	70
48	$(CH_3)_2N$–		B(MeOH)	MeOH/H_2O	113–114	287	17,500	1650	72
49	$(C_2H_5)_2N$–		B($CHCl_3$)	MeOH/H_2O	119–120	274	19,400	1645	35
50	$(CH_3)_2N$–		B(MeOH)	MeOH	58– 59	262	30,900	1660	58
51		H	C	MeOH/H_2O	128–129	–	–	1650	73

EXAMPLE 52.

5 - Diethylcarbamoyl - 3 - trans - p - methylsulphinylstyryl - 1,2,4 - oxadiazole.

Peracetic acid (1 ml., comml. *ca* 40%) was extracted with methylene chloride (5 ml.) and a portion (3.5 ml.) of this extract was added dropwise at room temperature to a stirred solution of 5 - diethylcarbonyl - 3 - trans - *p* - methylthiostyryl - 1,2,4 - oxadiazole (1.00g) in methylene chloride (50 ml.) during 70 minutes. The solution was shaken with saturated sodium hydrogen carbonate solution (20 ml.), and then water (20 ml), and dried Removal of the solvent under reduced pressure gave an off-white solid which was stirred with petroleum (50 ml, b.p. 40—60°), filtered off and dried under vacuum to give title compound (1.00 g.), m.p. 101.5—102°, $\lambda_{max.}$

(EtOH) 288.5 nm (ϵ 32,000), $\nu_{max.}$ ($CHBr_3$) 1650 ($CONEt_2$) and 970 cm.$^{-1}$ (trans CH=CH), τ ($CDCl_3$) values include 2.19, 2.82 (quartet J 16.5 Hz, trans CH=CH) and 7.25 (SOMe).

EXAMPLE 53.

5 - Diethylcarbamoyl - 3 - trans - p - methylsulphonylstyryl - 1,2,4 - oxadiazole.

Peracetic acid (3 ml. comml. *ca.* 40%) was extracted with methylene chloride (15 ml) and a portion (9.0 ml) of this extract was added dropwise at room temperature to a stirred solution of 5 - diethylcarbamoyl - 3 - trans-*p* - methylthiostyryl - 1,2,4 - oxadiazole (0.961g.) in methylene chloride (50 ml.) during 100 minutes. The solution was shaken with saturated sodium hydrogen carbonate solution (30 ml), and then water (20 ml), and dried Removal of the solvent under reduced pressure gave title compound (1.01 g.), m.p. 123—124°, $\lambda_{max.}$ EtOH) 284.5 nm (ϵ 34,900), $\nu_{max.}$ $CHBr_3$) 1650 $CONEt_2$) and 952 cm.$^{-1}$ (trans CH=CH), τ ($CDCl_3$) values include 2.17, 2.77 (quartet J 16.5, Hz, trans CH=CH) and 6.90 (SO_2Me).

EXAMPLE 54.

5 - Dimethylcarbamoyl - 3 - p - methylsulphinylstyryl - 1,2,4 - axodiazole.

5 - Dimethylcarbamoyl - 3 -*p* - methylthiostyryl - 1,2,4 - oxadiazole (700 mg.) was dissolved in methylene chloride (40 ml.). A solution of *ca.* 40% peracetic acid in methylene chloride (6.7% w/v; 2.8 ml.) was added dropwise at room temperature; the reaction was followed by thin-layer chromatography. The solvent was removed under reduced pressure and the residual solid was stirred with light petroleum (b.p. 40—60°), leaving the sulphoxide (670 mg., 90.7%), m.p. 136—137°. A sample recrystallised from toluene had m.p. 137—138°, $\lambda_{max.}$ (EtOH) 226, 288.5, and 305 nm, (ϵ 13900, 33200, and 21500) $\nu_{max.}$ ($CHBr_3$) 317 (C_6H_4), 972 (*trans*—CH=CH), 1043 (S→ O), 1660 cm.$^{-1}$ (CON<).

EXAMPLE 55.

5 - Diethylcarbamoyl - 3 - p - methoxystyryl-1,2,4 - oxadiazole.

5 - Ethoxycarbonyl - 3 - *p* - methoxystyryl-1,2,4 - axodiazole (1.25 g.) was suspended in dry methanol (5 ml.) and diethylamine (7.25 ml.) was added. The mixture was heated under reflux for 1 hour, when a solution was obtained. The solvent was removed under reduced pressure and the residual oil was dissolved in methanol and treated with charcoal. Evaporation of the filtrate left an oil, which was recrystallised from aqueous methanol to give the amide (1.199 g., 87.4%), m.p. 69—70°, $\lambda_{max.}$ (EtOH) 225.5 300 (infl.) and 308 nm. (ϵ 15400, 24400 and 25000), ν_{max} ($CHBr_3$) 820 (C_6H_4), 970 (*trans*—CH=CH), 1650 (CO.N<),

EXAMPLE 56.

trans - 5 - Diethylcarbamoyl - 3 - (5 - nitrofur - 2 - ylvinyl) - 1,2,4 - oxadiazole.

trans - 5 - Ethoxycarbonyl - 3 - (5 - nitrofur - 2 - ylvinyl) - 1,2,4 - oxadiazole (332 mg.) was heated under reflux with diethylamine (5 ml.) for 30 min. to give a deep red solution. Evaporation gave a red solid; recrystallisation from methanol (3 ml.) gave trans-5 - diethylcarbamyl - 3 - (5 - nitrofur - 2 - ylvinyl) - 1,2,4 - oxadiazole (208 mg., 57%), m.p. 118—119°, $\lambda_{max.}$ (EtOH) 240 and 349 nm. (ϵ 18,600 and 19,900), $\nu_{max.}$ ($CHBr_3$) 1665 ($CONEt_2$), 1510, 1350 (NO_2) and 960 cm.$^{-1}$ (trans CH=CH).

EXAMPLE 57.

Tablet

3 - α - naphthyl - 5 - diethylcarbamoyl - 1,2,4 - oxadiazole	500 mg.
Lactose	60 mg.
Gum Acacia	30 mg
Magnesium stearate	10 mg

The active ingredient was taken up in sufficient water to form a granulating fluid and the pH value adjusted to about 5.0 with the aid of citric acid. The gum acacia was dissolved in the same solution and this solution was used to granulate the lactose. The granules were passed through a 20 mesh (B.S.) sieve, dried, lubricated with the magnesium stearate and compressed.

EXAMPLE 58.

Tablet

Tablets were prepared as described in Example 57 using half quantities of excipients and 250 mg. per tablet of 3 - *p* - methylthiostyryl - 5 - diethylcarbamoyl - 1,2,4 - oxadiazole as active ingredient.

EXAMPLE 59.

Hard gelatin capsules

3 - α - naphthyl - 5 - diethylcarbamoyl-1,2,4 - oxadiazole	250 mg
Lactose	47 mg
Magnesium stearate	3 mg

The active ingredient and the lactose were blended together homogeneously. The mag-

nesium stearate was also blended in to provide good flow properties and the powder distributed into hard gelatin capsules so that each contained 250 mg. of the active ingredient.

EXAMPLE 60.

Eye Drops (Oily)

3α - naphthyl - 5 - diethylcarbamoyl-1,2,4 - oxadiazole		0.1 % w/v
Castor oil	to	100%

The active ingredient was reduced to a fine state by sub-division to a particle size of less than 10μ. The castor oil was sterilised by heating in a hot air oven at 160° C. The active ingredient was sterilised and dispersed in the sterile castor oil to yield a homogeneous mixture.

EXAMPLE 61.

Eye Drops (aqueous)

5 - diethyl carbamoyl - 3 - biphenylyl-1,2,4 - oxadiazole		0.1%
Sodium chloride		0.9%
Phenyl ethanol		0.4%
Benzalkonium chloride		0.002%
Water (for injection)	to	100%
Methyl cellulose	a sufficient amount to yield a final product with a viscosity of not less than 3000 centistokes.	

The methyl cellulose, sodium chloride, phenyl ethanol and benzalkonium chloride were dissolved in the water and sterilised by heating in a sealed container in an autoclave. The sterile micro-fine (particle size $< 10\mu$) active ingredient was then suspended in the sterile vehicle.

EXAMPLE 62.

Eye Ointment

3αnaphthyl-5-diethylcarbamoyl-1,2,4-oxadiazole		0.1%
Neomycin sulphate		0.5%
Liquid paraffin		20.0%
Soft paraffin	to	100.0%

The paraffins were mixed, melted and strained, and were then sterilised by heating in a hot air oven at 160° C. The sterile micro-fine (particle size $< 10\mu$) active ingredient and neomycin sulhpate were then suspended and homogeneously dispersed in the paraffin.

EXAMPLE 63.

Nasal Spray

3α-naphthyl-5-diethylcarbamoyl-1,2,4-oxadiazole		0.1%
Methyl cellulose		0.5%
Glycerin		30.0%
Sodium chloride		0.5%
Nipa 82121		0.05%
Distilled water	to	100.0%

('Nipa' is a trade Mark)

The Nipa 82121, which is a mixture of the methyl, ethyl, propyl and butyl esters of para hydroxy benzoic acid, was dissolved in hot water, and the solution cooled to room temperature. The methyl cellulose, glycerin and sodium chloride were then dissolved in the Nipa 82121 solution. The solution was clarified by filtration and the micro-fine active ingredient (particle size $< 10\mu$) suspended in it.

EXAMPLE 64.

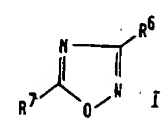
Tablets

5 - Diethylcarbamoyl - 3 - *trans* - *p* - methylsulphinylstyryl - 1,2,4 - oxadiazole	250 mg
Polyethylene Glycol 6000	7.5 mg
Magnesius Stearate	2.5 mg

The active ingredient is ground to a powder having a particle size between 1 and 10 microns, It is then granulated with the aid of a chloroform solution of the polyethylene glycol by passing it through a No. 12 mesh British standard sieve, and dried *in vacuo*. The dried granulate is passed through a No. 16 mesh British standard sieve. The granulate is then blended with the magnesium stearate which acts as a lubricant and compressed on 8 mm punches, preferably having a breakline. Each tablet weighs 260 mg. These tablets may if desired be film-coated in conventional manner.

WHAT WE CLAIM IS:—

1. 1,2,4 - Oxadiazole compounds of the general formula



I

where R^6 represents R, where R represents a hydrogen atom or an aliphatic cycloaliphatic, araliphatic, aryl or heterocyclic group; or a carbamoyl group of the formula—$CONR^1R^2$ where R^1 and R^2, which may be the same or different, represent hydrogen atoms, or alkyl, alkenyl or alkynyl groups (or such groups substituted by a hydroxy group) or cycloali-

phatic, araliphatic or aryl groups or, together with the intervening nitrogen atom, represent a heterocyclic ring; and R' represents R, where R is as defined above or a carbamoyl group of the formula —$CONR^3R^4$, where R^3 and R^4 are as defined above, for R^1 and R^2; provided that at least one of R^6 and R' is an N-substituted carbamoyl group.

2. Compounds as claimed in claim 1 wherein R is a mono- or bicyclic aryl group or an aralkyl, aralkenyl or aralkynyl group, the aryl portions of which groups being unsubstituted or a substituted or unsubstituted alkyl, alkenyl alkoxy, C_{1-6} alkylthio, C_{1-6} alkyl-sulphinyl, C_{1-6} alkylsulphonyl, amino, acylamino, cyano, thiocyanato or nitro groups or halogen atoms; or a substituted or unsubstituted alkyl, alkenyl or alkynyl group; or a 5- or 6-membered heterocyclic group.

3. Compounds as claimed in claim 1 wherein R is a tolyl, α-naphthyl, biphenylyl, *p*-methoxyphenyl, *p*-chlorophenyl, *p*-methylsulphinylstyryl or *p*-methylthiostyryl group, or a hydrogen atom.

4 Compounds as claimed in claim 1 wherein R is a phenyl, benzyl, phenethyl, phenylethynyl, styryl, naphthyl, furyl, thienyl, pyridyl, methyl, ethyl, allyl, ethnyl or propargyl group.

5. Compounds as claimed in any one of the preceding claims wherein R^1, R^2, R^3 or R^4 is C_{1-6} alkyl, alkenyl, alkynyl, monocyclic or caged cycloalkyl, monocyclic aryl, aralkyl, aralkenyl or aralkynyl group, or wherein R^1 and R^2 or R^3 and R^4 together with the intevening nitrogen atom is a heterocyclic group having 5—10 ring members.

6. Compounds as claimed in any one of the preceding claims wherein R^1 and R^2 or R^3 and R^4 are both methyl, ethyl or *n*-propyl groups, or, together with the intervening nitrogen atom, are a piperadino group, or wherein R^1, R^2, R^3 or R^4 is an adamantyl group.

7. Compounds as claimed in any one of claims 1 to 5 wherein R^1, R^2, R^3 or R^4 is a methyl, ethyl, propyl, *n*-butyl, *t*-butyl, 2-hydroxyethyl, allyl, propargyl, phenyl, benzyl or cyclohexyl group, or wherein R^1 and R^2 or R^3 and R^4 together with the intervening nitrogen atom is a piperidino, morpholino, pyrrolidin - 1 - yl, piperazin - 1 - yl, 4 - (C_{1-6}) alkylpiperazin - 1 - yl or 3 - azabicyclo - 3,2,2,) - nonan - 3 - yl - group.

8. 3 - Adamantylcarbamoyl - 1,2,4 - oxadiazole.

9. 5 - Diethylcarbamoyl - 3 - α - naphthyl - 1,2,4 - oxadiazole.

10. 5 - Diethylcarbamoyl - 3 - *p* - methoxyphenyl - 1,2,4 - oxadiazole.

11. 5 - *p* - Chlorophenyl - 3 - diethylcarbamoyl - 1,2,4 - oxadiazole.

12. 5 - α - Naphthyl - 3 - dimethylcarbamoyl - 1,2,4 - oxadiazole.

13. 5 - Diethylcarbamoyl - 3 - trans - *p* - methylthiostyryl - 1,2,4 - oxadiazole.

14. 5 - Piperidocarbonyl - 3 - *p* - methoxyphenyl - 1,2,4 - oxadiazole.

15. 5 - Piperidinocarbamoyl - 3 - α - naphthyl - 1,2,4 - xadiazole.

16. 5 - Dimethylcarbamoyl - 3 - *p* - methoxyphenyl - 1,2,4 - oxadiazole.

17. 5 - Dimethylcarbamoyl - 3 - α - naphthyl - 1,2,4 - oxadiazole.

18. 5 - di - *n* - propylcarbamoyl - 3 - α - naphthyl - 1,2,4 - oxadiazole.

19. 5 - *p* - Tolyl - 3 - dimethylcarbamoyl-1,2,4 - oxadiazole.

20. 5 - Diethylcarbamoyl - 3 - trans - *p* - methylthiostyryl - 1,2,4 - oxadiazole.

21. 3 - Biphenylyl - 5 - diethylcarbamoyl - 1,2,4 - oxadiazole.

22. 5 - Diethylcarbamoyl - 3 - trans - *p* - methylsulphinylstyryl - 1,2,4 - oxadiazole.

23. 5 - Diethylcarbamoyl - 3 -(5 - nitrofur - 2 - ylvinyl) - 1,2,4 - oxadiazole.

24. A compounds as claimed in claim 1 substantially as described herein with reference to any one of Examples 1 to 37, and 41 to 53.

25. A compound as claimed in claim 1 substantially as described herein with reference to any one of Examples 38 to 40 and 54 to 56.

26. A pharmaceutical or veterinary composition comprising a compound as claimed in claim 1 and a pharmaceutical or veterinary carrier or excipient.

27. A composition as claimed in claim 26 in a form suitable for oral, topical or rectal administration.

28. A composition as claimed in claim 26 or claim 27 wherein the excipient or carrier is a solid and the composition also includes a binder, lubricant, stabiliser, coating, flavouring or colouring, or wherein the excipient or carrier is a liquid and the compositions also include a suspending, emulsifying, stabilising, preserving, sweetening, flavouring, colouring, dispersing, solubilising or buffering agent.

29. A composition as claimed in any one of claims 26 to 28 in dosage unit form.

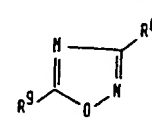
30. A composition as claimed in claim 29 wherein each dosage unit contains 0.05 to 4 g of the said compound.

31. A composition as claimed in claim 29 wherein each dosage unit contains 2 to 500 mg of the said compound.

32. A pharmaceutical composition substantially described herein with reference to any one of Examples 57 to 59.

33. A pharmaceutical composition substantially as described herein with reference to any one of Examples 60 to 64.

34. A process for the preparation of a compound as claimed in claim 1 wherein a compound of the general formula.



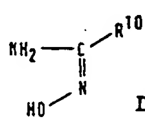
II

(wherein R^8 and R^9, which may be the same or different, represent R or a group of the formula —$CONR^1R^2$ or —$CONR^3R^4$ where R, R^1, R^2, R^3 and R^4 are as defined in claim 1, or a carboxylic acid group or a reactive derivative thereof, provided that at least one of R^8 and R^9 is a carboxylic acid group or a reactive derivative thereof) is reacted with a nitrogen base of the formula R^1 R^2 NH or R^3R^4NH (where R^1, R^2, R^3 and R^4 are as defined in claim 1) or, where a carboxylic acid of the formula II is used, with an isocyanate of the formula R^1NCO or R^3NCO.

35. A process as claimed in claim 34 wherein the reactive derivative is an ester, an acid halide or an azide.

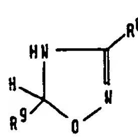
36. A process for the preparation of a compound as claimed in claim 1 or for the preperation of a compound of the formula II as defined in claim 34, which process comprises first reacting a correspondingly substituted amidoxime with an acylating agent and then cyclising the O-acyloxyamidoxime produced.

37. A process as claimed in claim 36 wherein an amidomixe of the general formula


III

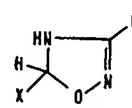
(where R^{10} represents R as defined in claim 1 or an esterified carboxylic acid group) is reacted with an oxalic acid derivative of the formula HalCOX where Hal represents a halogen atom and X is a group R or a group —$CONR^3R^4$ (as defined in claim 1) or an esterified carboxylic acid group to yield (a) a compound as claimed in claim 1 in which R^6 represents R and R^7 represents a group —$CONR^3R^4$ or (b) a compound of the formula II as defined in claim 34 wherein R^8 represents R or an esterified carboxylic acid group and R^9 represents an esterified carboxylic acid group; or (c) a compound of the formula II as defined in claim 34 in which R^8 represents an esterified carboxylic acid group and R^9 represents a group —$CONR^3R^4$ or a group R as defined in claim 1.

38. A process for the preparation of a compound as claimed in claim 1 which comprises oxidising an oxadiazoline of the general formula


V

wherein R^8 represents R as defined in claim 1 or a group —$CONR^1R^2$ and R^9 represents a group —$CONR^3R^4$ or R where R, R^1, R^2, R^3 and R^4 have the meanings given in claim 1.

39. A process for the preparation of a compound of the formula V which comprises reacting a compound of the formula


IV

(where X is as defined in claim 37 and R^{10} represents R, an esterfied carboxylic acid group or a group —$CONR^1R^2$, and at least one of X and R^{10} is an esterified carboxylic acid group) with an amine of the formula HNR^3R^4, where R^1, R^2, R^3 and R^4 are as defined in claim 1.

40. A process for the preparation of a compound of the formula IV as defined in claim 39 which comprises reacting a compound of the formula III as defined in claim 37 but wherein R^{10} represents R as defined in claim 1, an esterfied carboxylic acid group or a group —$CONR^1R^2$, with a glyoxylic acid derivative of the formula HCOX where X is as defined in claim 37.

41. A process for the preparation of a compound as claimed in claim 1 (wherein R^7 represents a hydrogen atom and R^6 a group —$CONR^1R^2$) or compound of the formula II (as defined in claim 34 wherein R^9 represents a hydrogen atom and R^8 represents an esterified carboxylic acid group) which comprises reacting a compound of the formula III (as defined in claim 37 but wherein R^{10} represents an esterified carboxylic acid group or a group —$CONR^1R^2$) with an orthoformate in the presence of a Lewis acid or with formyl fluoride.

42. A process as claimed in claim 41 wherein a dialkyl acetal of dimethylformamide or dimethylformamide/phosphorus oxychloride is used instead of an orthoformate of formyl fluoride.

43. A process for the preparation of a compound as claimed in claim 1 wherein R is an aryl or araliphatic group substituted by an alkyl sulphinyl or alkylsulphonyl group, which comprises oxidising a corresponding arlkylthio compound.

44. A process for the preparation of a compound as claimed in claim 1 substantially as described herein with reference to any one of Examples 1 to 37 and 41 to 53.

45. A process for the preparation of a compound as claimed in claim 1 substantially as described herein with reference to any one of Examples 38 to 40 and 54 to 56.

46. A compound as defined in claim 1 when prepared by a process as claimed in any one of claims 34 to 45.

47. An oxidiazoline of the general formula V as defined in claim 38.

For the Applicant.
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Printed for Her Majesty's Stationery Office by the Courier Press, Leamington Spa, 1975.
Published by the Patent Office, 25 Southampton Buildings, London, WC2A 1AY, from which copies may be obtained.

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